Diabetes Management Strategies in Intensive Care Settings

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KEYWORDS

• Critical illness • Intensive care • Hyperglycemia • Hypoglycemia • Blood glucose • Insulin • Parenteral nutrition • Diabetes

KEY POINTS

- Blood glucose concentrations in critically ill patients exhibit a U-shaped relationship with outcome, with the lowest risk of mortality associated with normal blood glucose levels.
- In all critically ill patients, severe and iatrogenic hyperglycemia should be prevented, as well as hypoglycemia and large blood glucose fluctuations.
- Safe and tight blood glucose control requires accurate and frequent blood glucose measurements and avoiding insulin boluses.
- The ideal blood glucose target for critically ill patients is context-dependent, depending on the accuracy and frequency of the glucose measurements, the insulin titration protocol, and the nutritional strategy.
- Future research should focus on strategies that can improve the quality of blood glucose control and study whether particular subgroups of patients have a differential response to different levels of blood glucose control.

INTRODUCTION

Critically ill patients often develop hyperglycemia, which has been associated with poor outcomes. Indeed, multiple observational studies have reported a U-shaped relationship between blood glucose concentrations in the intensive care unit (ICU) and the

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Abbreviations	
CGM	continuous glucose monitoring
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
ICU	intensive care unit
RCT	randomized controlled trial
SGLT2i	sodium-glucose cotransporter-2 inhibitors
TGC	tight glucose control

risk of mortality, with the nadir occurring in the age-adjusted normal fasting range.[1–3] Nevertheless, proof of causality requires a randomized controlled trial (RCT), because the degree of hyperglycemia is closely associated with illness severity. Landmark RCTs support a potential causal relationship, as avoiding severe hyperglycemia improved outcomes in critically ill patients.[4–7] However, safe implementation of tight glucose control requires an accurate protocol that minimizes the risk of hypoglycemia.[8] In this review, we summarize evidence from landmark RCTs, mechanisms underlying organ protection, strategies to improve blood glucose control, and future perspectives.

RESULTS FROM LANDMARK RANDOMIZED CONTROLLED TRIALS

In 3 landmark RCTs performed in Leuven (N = 3448), Belgium, tight glucose control (TGC) with intensive insulin therapy, targeting age-adjusted normal fasting blood glucose concentrations (50–80 mg/dL [2.8–4.4 mmol/L] for infants, 70 to 100 mg/dL [3.9–5.6 mmol/L] for children aged older than 1 year, and 80 to 110 mg/dL [4.4–6.1 mmol/L] for adults) significantly reduced morbidity and mortality in critically ill patients as compared with tolerating hyperglycemia up to the renal threshold for glucosuria (215 mg/dL [11.9 mmol/L]).[4–6] Indeed, TGC significantly reduced vital organ dysfunction as well as the incidence of infections and ICU-acquired weakness, thereby leading to a shorter ICU stay and improved survival.[4–6] In critically ill adults, mortality benefit persisted up to 2 years after randomization,[9] and in critically ill children, TGC also improved 4 year neurocognitive outcomes, despite an increased risk of hypoglycemia.[10] The intervention was also shown to reduce costs.[11]

Subsequent mechanistic studies attributed the clinical benefit to a protection against glucose toxicity rather than to glucose-independent effects of insulin (**Fig. 1**).[12–14] Cells with insulin-independent (ie, glucose-concentration-dependent) glucose uptake appeared particularly vulnerable to hyperglycemic damage. Indeed, in an animal model, maintaining normoglycemia prevented the accumulation of potentially toxic glucose metabolites, which was associated with less mitochondrial damage and improved function of vital organs and immune cells, as well as improved survival. In contrast, increased insulin doses were not protective in the animal model.[12–14] Likewise, in a secondary analysis of the Leuven RCTs, lowered blood glucose concentrations were associated with improved outcomes in a dose-dependent manner. In contrast, increased insulin doses were associated with an opposite effect.[15,16] Prevention of glucose toxicity may also explain why the effect size of the intervention in the Leuven RCTs increased with prolonged exposure. Indeed, the observed benefit was greater in long-stay ICU patients than in shorter stay patients.[4,5] Hence, the pioneer clinical and experimental studies performed in Leuven suggested a dose-dependent impact of glucose-lowering on outcomes, with the highest efficacy of the intervention if glucose concentrations were maintained within the normal fasting range. Yet, such intervention inherently increases the risk of hypoglycemia. To minimize this risk, insulin was only administered through continuous

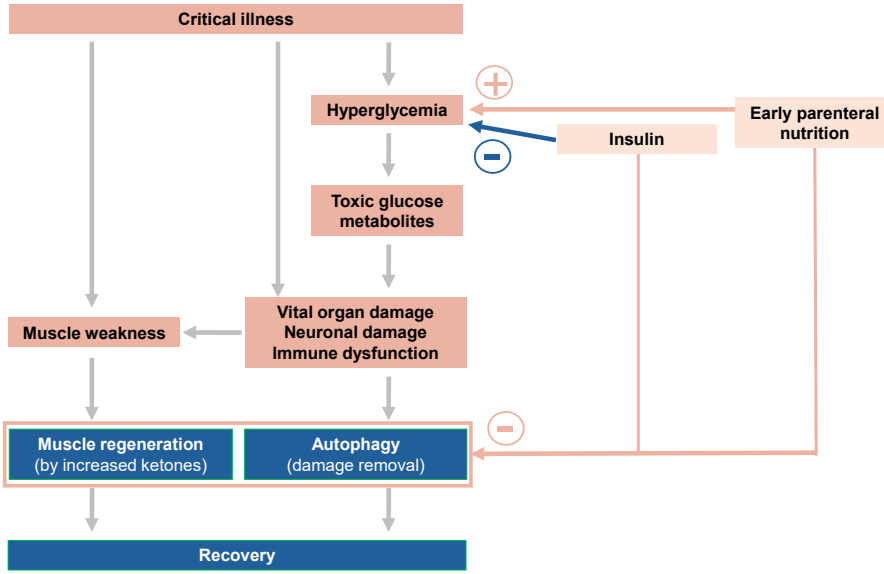

Fig. 1. Mechanisms of organ protection by tight glucose control and avoiding early parenteral nutrition. Mechanistic studies have shown that the protective effects of tight glucose control with intensive insulin therapy are mediated by preventing glucose toxicity and the ensuing accumulation of toxic glucose metabolites that associate with damage to vital cells. Early full nutritional support was shown to be harmful at least in part by suppressing autophagy and ketogenesis. Autophagy is an important cellular repair process that clears macromolecular cell damage, and increased ketone availability has been linked to improved muscle regeneration. Insulin therapy may have both positive and negative effects on vital organ damage: indirect positive effects through reducing hyperglycemia and associated metabolic damage, and direct negative effects through suppressing autophagy and ketogenesis.

intravenous infusion via a central venous line, and glucose measurements were frequently performed, predominantly on arterial blood using an accurate blood gas analyzer.[4–6] Moreover, all patients in the Leuven RCTs received early parenteral nutrition to supplement insufficient enteral nutrition as part of standard care, which also reduced the risk of hypoglycemia.[4–6,17,18]

Soon after the Leuven RCTs, tighter glucose control regimens were rapidly adopted, and several single-center RCTs and observational studies associated a benefit with this intervention.[19–24] Nevertheless, the mortality benefit was not confirmed by multicenter RCTs.[25–31] Although this could be explained by a lack of power resulting from lower glucose targets in the control group, and, in some RCTs, by a suboptimal glucose control protocol, with a high incidence of hypoglycemia in the intervention group, several investigators questioned whether the benefit of TGC could be specific to the nutritional context of providing early parenteral nutrition.[32] Indeed, in the absence of solid evidence guiding the ideal nutritional strategy, this practice was not uniformly applied, and alternative nutritional strategies coexisted. European guidelines at that time recommended avoiding any fasting in critical illness by initiating early enteral and/or parenteral nutrition, based on observational studies that had associated a progressive caloric deficit with poorer outcomes.[33] Nevertheless, these observational studies are inherently confounded by illness severity, as less severely ill patients tend to have better feeding tolerances. Although guidelines in North America advised starting early enteral

nutrition, they recommended tolerating underfeeding in the first week in the ICU, if enteral nutrition was not possible or tolerated, and to initiate parenteral nutrition only after 1 week in the ICU.[34] The latter recommendations were based on concerns about potentially increased infectious complications with parenteral nutrition. As large-scale RCTs studying the optimal nutritional strategy in acute severe illness were lacking, the Leuven investigators initiated, following the glucose control RCTs, 2 multicenter RCTs to investigate the impact of early versus delayed initiation of parenteral nutrition.[17,18] In the EPaNIC (N = 4640) and PEPaNIC (N = 1440) RCT in critically ill adults and children, respectively, early parenteral nutrition was shown to prolong ICU dependency as compared with withholding parenteral nutrition until 1 week after ICU admission.[17,18] Subsequent RCTs comparing different doses and routes of early nutritional support have suggested that harm by early parenteral nutrition in (P)EPaNIC is explained by an increased nutritional dose, rather than the parenteral route being harmful in the short term.[35–38] In line with this, secondary analyses of both EPaNIC and PEPaNIC also found dose-dependent harm associated with early nutritional support.[39,40] Mechanistic studies have attributed harm by early full nutrition to a suppression of beneficial repair processes activated by fasting, including autophagy and ketogenesis (see **Fig. 1**).[41–44] Indeed, autophagy has been identified as a crucial process to clear critical illness-induced cellular damage, and increased ketone availability has been linked to improved muscle regeneration in critical illness.[41–45] Hence, nutritional practices have shifted to more restricted nutrition in the acute phase of critical illness, including avoidance of early parenteral nutrition.[46]

The current feeding standard not only increases the risk of hypoglycemia but also implies less severe hyperglycemia, with less anticipated metabolic damage in a context of more active damage removal processes.[17,18] Hence, the efficacy and safety of TGC in the context of withholding early parenteral nutrition needed to be studied. In this regard, the large multicenter NICE-SUGAR RCT (N = 6104) showed, as compared with keeping blood glucose below 180 mg/dL (10.0 mmol/L), increased mortality by TGC in patients not receiving early parenteral nutrition, which was subsequently attributed to the elevated risk of severe hypoglycemia.[47,48] Yet, the NICE-SUGAR protocol allowed insulin boluses, used potentially inaccurate glucometers, and capillary and venous measurements that are potentially unreliable in patients with poor tissue perfusion and patients receiving intravenous glucose infusion, respectively.[49] All this may have contributed to the observed 14 fold higher risk of severe hypoglycemia (<40 mg/dL [2.2 mmol/L]), which was likely an underestimation of the true incidence, because of the inaccurate measurements.[50] The high incidence of hypoglycemia could theoretically have offset any benefit of preventing less severe hyperglycemia. Moreover, inaccurate glucose measurements and insulin boluses likely induced high blood glucose variability, which also has been associated with impaired outcomes.[3] The harmful effects of TGC in NICE-SUGAR illustrate the complexity of the intervention and underscore the importance of considering the glucose control protocol before adopting a particular blood glucose target. This becomes especially important with tighter targets and with current nutritional strategies that avoid severe feeding-induced hyperglycemia in the acute phase.

To improve the quality of TGC and minimize the risk of hypoglycemia during relative fasting, different research groups have developed and validated insulin titration protocols, with differing designs and performances.[51] One of the most validated computerized algorithms is the LOGIC-Insulin algorithm, which advises on the insulin dose (glucose bolus in case of severe hypoglycemia), and the timing of the next glucose measurement, based on the evolution of blood glucose concentrations, changes in nutritional intake, and use of steroids, among others.[52,53] In a multicenter validation

RCT in patients not receiving early parenteral nutrition, LOGIC-Insulin-guided TGC led to superior glucose metrics as compared with nurse-guided control, with a higher time in target range and no increase in hypoglycemic events.[53] However, whether this improves clinical outcomes compared with liberal blood glucose control remained to be studied, for which the multicenter TGC-Fast RCT (N = 9230) was designed.[54] In TGC-Fast, as expected in a context of withholding early parenteral nutrition, blood glucose concentrations were less elevated than in the previous Leuven studies.[7] In the tight group, blood glucose concentrations were well controlled within the normal range, without increasing the risk of hypoglycemia. The intervention did not affect the duration of ICU dependency (primary endpoint) or mortality (safety endpoint), but was associated with less severe acute kidney injury and cholestatic liver dysfunction, suggesting a smaller but potentially relevant benefit as compared with the initial RCTs.[7]

IS THERE ANY DIFFERENTIAL RESPONSE TO GLUCOSE CONTROL STRATEGIES IN SUBGROUPS OF PATIENTS?

Observational studies have suggested potential heterogeneity of treatment effects for patients with diabetes, neuro-ICU patients, and patients with severe inflammation. Indeed, the U-shaped association between blood glucose concentrations and outcome that is seen in nondiabetic patients is slightly flattened and shifted to the right in patients with diabetes, especially in those with poorly controlled diabetes before ICU admission, which could point to adaptations to chronic hyperglycemia.[3,55] In line with this, patients with poorly controlled diabetes can have an elevated threshold for hypoglycemia symptoms, which could imply that normalizing blood concentrations may be deleterious in such patients.[55] However, solid evidence supporting a different blood glucose target in patients with diabetes is lacking. In TGC-Fast, there was no heterogeneity of treatment effects observed in patients with diabetes (N = 1888) versus nondiabetes patients (N = 7342), with a protocol that avoided hypoglycemia.[7] However, subgroup analyses were only performed for the primary and safety endpoint, and they did not take into account the quality of preadmission blood glucose control, as indicated by the hemoglobin A1c (HbA1c).[7] The multicenter CONTROLING RCT, the largest RCT that investigated the impact of individualized HbA1c-guided glucose control in critically ill patients (N = 2075) found no benefit of targeting the average preadmission blood glucose concentration as compared with a conventional target (<180 mg/dL [<10.0 mmol/L]).[56] However, CONTROLING allowed late randomization, and a considerable number of patients had intermediate Hb1A1c levels, leading to considerable overlap in achieved blood glucose concentrations between both groups. Hence, the study is likely underpowered to detect or exclude a meaningful clinical benefit by individualized blood glucose control.[57] On the other hand, evidence indicates that severe hyperglycemia should be avoided in all patients, including patients with diabetes. In the LUCID RCT in ICU patients with type 2 diabetes (N = 419), very liberal blood glucose control (180–252 mg/dL [10.0–14.0 mmol/L]) was associated with a 4.6% increase in 90 day mortality as compared with conventional control with a target of 108 to 180 mg/dL (6.0–10.0 mmol/L).[58] Although the mortality difference did not reach statistical significance, potentially due to a lack of power, these results do not support accepting severe hyperglycemia for patients with and without a known diagnosis of diabetes mellitus.

A second subgroup of patients that may respond differently to glucose control strategies is the subgroup of neuro-ICU patients, because neurons and astrocytes may be particularly vulnerable to damage induced by both hyperglycemia and hypoglycemia.[7] In TGC-Fast, the subgroup of neuro-ICU patients was the only patient population in

whom significant heterogeneity of treatment was observed. In this large subgroup (N = 1053), there was a potential mortality benefit by TGC, which was not observed in the total study population.[7] Ongoing mechanistic studies and long-term follow-up of these patients will provide insight into whether strictly preventing hyperglycemia had neuroprotective effects. Importantly, in TGC-Fast, hypoglycemia was carefully prevented by use of the LOGIC-Insulin algorithm, so one should be careful not to extrapolate TGC-Fast findings to other protocols with a different quality of blood glucose control.

Third, evidence suggests that patients with acute hyperinflammation may particularly benefit from TGC. Indeed, in secondary analyses of 2 pediatric RCTs, the benefit of TGC was observed only in patients with severe inflammation at baseline.[59,60] Nevertheless, the achieved difference in blood glucose concentrations was also substantially larger (38 mg/dL [2.1 mmol/L] vs 9 mg/dL [0.5 mmol/L]),[59] so it remains unclear whether patients with hyperinflammation do have a particular vulnerability to hyperglycemic damage, or whether the perceived differential effect is mainly explained by more severe insulin resistance and hyperglycemia in these patients, and a lack of power to detect a smaller potential benefit in patients without hyperinflammation. Also, it remains unclear whether these findings can be extrapolated to critically ill adults. In TGC-Fast, there was no heterogeneity of treatment effect between patients with or without sepsis, which could argue against such potential treatment heterogeneity.[7] Future research should further investigate potential endotypes in critically ill adults, which could pave the way for personalized medicine.

IMPLICATIONS FOR CLINICAL PRACTICE

The different results from the landmark RCTs on TGC illustrate that the effect of the intervention is context-dependent.[8] Mortality benefit by the intervention was only shown in a context of severe, iatrogenic hyperglycemia induced by early parenteral nutrition, which is currently avoided after large RCTs have shown harm by such intervention, even when parenteral nutrition-induced hyperglycemia is treated. The lower effect size by TGC in the absence of early parenteral nutrition suggests to at least prevent severe iatrogenic hyperglycemia by avoiding early full nutritional support.[61] Future research should investigate whether these findings can be extrapolated to other scenarios of iatrogenic hyperglycemia, such as steroid-induced hyperglycemia, which frequently occurs in critically ill patients. Anyway, the harm associated with iatrogenic hyperglycemia should question the liberal use of steroids, that is, when administered in the absence of a clear evidence-based indication.

The discordant results between NICE-SUGAR and TGC-Fast, both performed in a context of not giving early parenteral nutrition, suggest that safe glucose control requires accurate tools to avoid hypoglycemia and large blood glucose fluctuations.[61] In the absence of such tools, TGC increased mortality risk, whereas it was associated with reduced morbidity when performed with a validated protocol that avoided severe hypoglycemia.

Hence, the ideal blood glucose target is likely context-dependent (**Fig. 2**).[61] To avoid iatrogenic hyperglycemia and other associated harm, we recommend avoiding early full nutrition in all critically ill patients, and initiating parenteral nutrition only after 1 week in the ICU if the feeding target cannot be reached via the oral or enteral route. Safe blood glucose control additionally requires accurate glucose measurements and avoidance of insulin boluses. If possible, we recommend measuring blood glucose in arterial blood using a blood gas analyzer, as it provides an accurate, instantaneous measurement and simultaneously measures potassium, the latter to prevent and treat insulin-induced hypokalemia. We recommend treating hyperglycemia with short-acting insulin,

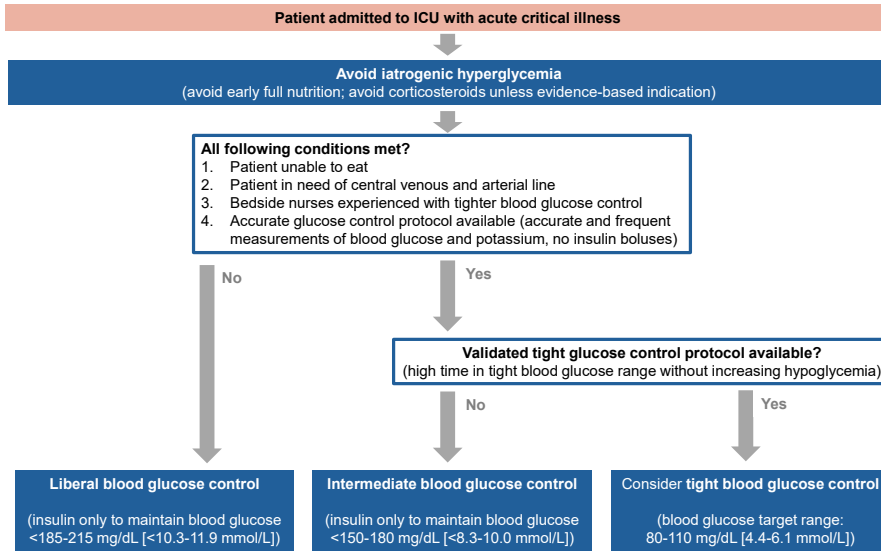
Patient admitted to ICU with acute critical illness
Avoid iatrogenic hyperglycemia
(avoid early full nutrition; avoid corticosteroids unless evidence-based indication)
All following conditions met?
1. Patient unable to eat
2. Patient in need of central venous and arterial line
3. Bedside nurses experienced with tighter blood glucose control
4. Accurate glucose control protocol available (accurate and frequent measurements of blood glucose and potassium, no insulin boluses)
No
Yes
Validated tight glucose control protocol available?
(high time in tight blood glucose range without increasing hypoglycemia)
No
Yes
Liberal blood glucose control
(insulin only to maintain blood glucose <185-215 mg/dL [<10.3-11.9 mmol/L])
Intermediate blood glucose control
(insulin only to maintain blood glucose <150-180 mg/dL [<8.3-10.0 mmol/L])
Consider tight blood glucose control
(blood glucose target range: 80-110 mg/dL [4.4-6.1 mmol/L])

Fig. 2. Proposed algorithm for selecting the blood glucose target in ICU. The algorithm visualizes how to adapt blood glucose targets according to the specific context. (Gunst, J., Umpierrez, G.E. & Van den Berghe, G. Managing blood glucose control in the intensive care unit. Intensive Care Med 50, 2171–2174 (2024). https://doi.org/10.1007/s00134-024-07687-y.)

administered by continuous intravenous infusion (without boluses) through a central venous line with a syringe pump, in order to avoid large blood glucose fluctuations and hypoglycemia. If the previous requirements are not feasible, if the patient does not need an arterial and central venous line, if the patient is able to eat, and/or the team is not experienced with TGC, we recommend to tolerate hyperglycemia up to a liberal threshold (185–215 mg/dL [10.3–11.9 mmol/L]). Otherwise, we recommend stricter blood glucose control, targeting blood glucose below 150 to 180 mg/dL (8.3–10.0 mmol/L). We recommend to consider tight blood glucose targets (80–110 mg/dL [4.4–6.1 mmol/L] for adult patients) only if tight control can be achieved with a validated protocol that avoids severe hypoglycemia (<40 mg/dL [<2.2 mmol/L]). In the absence of new evidence, we do not recommend differential blood glucose targets in particular subgroups of patients. If, at ICU discharge, persistent insulin is needed to prevent severe hyperglycemia, we recommend to switch intravenous insulin to maintenance treatment in consultation with an endocrinologist or a diabetes specialist.[61]

STRATEGIES TO OPTIMIZE THE QUALITY OF BLOOD GLUCOSE CONTROL

Since aggregated RCT evidence suggests that TGC may be superior, provided that it can be achieved without inducing hypoglycemia, future research should aim at strategies that further improve the quality of blood glucose control and minimize the risk of hypoglycemia. These strategies include continuous glucose monitoring (CGM) and closed-loop glucose control, alternative glucose-lowering agents, and alternative nutritional strategies, whether or not combined with exercise, the latter of which is known to improve insulin sensitivity in non-ICU patients.[61]

Theoretically, CGM could greatly improve the quality and safety of glucose control.[62] Indeed, CGM could lead to preemptive or more rapid treatment of hypoglycemia and prevent substantial blood glucose fluctuations. A recent study suggested that CGM has improved trend accuracy compared with intermittent blood glucose

measurements, which may be particularly relevant for patients with highly fluctuating blood glucose concentrations.[63] However, CGM also has potential drawbacks in ICU patients, which preclude its widespread use. Apart from substantial costs and limited reimbursement in most health care systems, the accuracy of point measurements has been questioned, especially for subcutaneous sensors.[64] A recent systematic review found that for most subcutaneous sensors, point accuracy did not meet the consensus recommendations criteria for use in ICU settings, which may be partly related to altered tissue perfusion and substantial fluid shifts occurring in critical illness.[64] Also, subcutaneous sensors have an inherent lag time that should be considered, and this may hamper tight control. Therefore, intravascular sensors may be superior, although accuracy varies, and not all devices meet the consensus recommendations for use in the ICU.[64] Theoretically, CGM could be combined with insulin titration algorithms to achieve closed-loop glucose control. Interestingly, an RCT (N = 447) showed that TGC (80–110 mg/dL [4.4–6.1 mmol/L]) using a closed-loop system with an intravascular sensor reduced the incidence of infections in surgical ICU patients as compared with intermediate blood glucose control (139–180 mg/dL [7.7–10.0 mmol/L]).[65] Although these observations were obtained in a selected population of patients receiving early parenteral nutrition, the results clearly open perspectives for future research in patients not receiving early parenteral nutrition. In the absence of new evidence, we do not recommend routine use of CGM in critically ill patients.

An alternative way to improve blood glucose control and reduce the risk of hypoglycemia is the use of alternative strategies to lower blood glucose. Currently, short-acting insulin administered via continuous intravenous infusion is the preferred regimen for blood glucose control in ICU patients, to allow continuous adjustment of the dose and avoid large blood glucose fluctuations.[8,66] Nevertheless, insulin treatment inherently increases the risk of hypoglycemia, especially when nonvalidated treatment algorithms are used. Moreover, from a pathophysiological perspective, insulin suppresses autophagy and ketogenesis, which have been identified as mechanisms that explain the harm caused by early full nutrition (see **Fig. 1**).[46] In this regard, insulin therapy could be a double-edged sword: it could have (indirect) positive effects through reducing hyperglycemia-induced damage, and (direct) negative effects through suppressing cellular repair and increasing the risk of hypoglycemia.[8] Therefore, future research should focus on strategies that improve glucose control without requiring exogenous insulin. Candidate strategies include alternative glucose-lowering agents and alternative feeding strategies.

Regarding alternative glucose-lowering agents, a potential role of sodium-glucose cotransporter-2 inhibitors (SGLT2i) should be further investigated. In addition to lowering blood glucose and insulin requirements, SGLT2i could increase ketogenesis and activate autophagy.[67] The multicenter PROTECTION RCT (N = 507) showed that dapagliflozin reduced hyperglycemia and insulin need, as well as the need for renal replacement therapy in patients with acute organ dysfunction.[68,69] Although the latter was a secondary endpoint, this observation mimics the renoprotective effect observed in TGC-Fast,[7] which may support a protective role of normalizing blood glucose in ICU patients. Nevertheless, the efficacy and safety of SLGT2i need to be confirmed in adequately powered RCTs, especially since SGLT2i carry a risk of inducing euglycemic ketoacidosis in a context of relative starvation, for which these drugs are traditionally withheld in ICU patients.[68,70] In PROTECTION, this complication was carefully prevented through ensuring minimal glucose intake during dapagliflozin treatment.[68] Apart from SLGT2i, a second alternative to insulin may be the use of glucagon-like peptide-1 (GLP-1) agonists.[71] These drugs enhance insulin secretion in a glucose-dependent

manner, resulting in a considerably lower risk of hypoglycemia compared to insulin. Additionally, GLP-1 agonists reduce glucagon secretion and slow gastric emptying, which contribute to improved blood glucose control. Small RCTs in ICU patients have suggested that use of GLP-1 agonists can reduce insulin need, although larger trials are needed to confirm efficacy and safety.[71] In this regard, the suppressive effects on gastric emptying may be unwanted in ICU patients, who frequently have feeding intolerance. Finally, an RCT in 182 patients with type 2 diabetes undergoing cardiac surgery has studied the impact of sitagliptin, a dipeptidyl peptidase-4 inhibitor, which is also associated with a low risk of hypoglycemia. However, in the RCT, there was no clinical benefit of sitagliptin as compared with placebo. Moreover, sitagliptin did not prevent or reduce perioperative hyperglycemia and only reduced insulin need in the postacute phase after transitioning to subcutaneous insulin.[72]

Apart from alternative glucose-lowering drugs, fasting-mimicking interventions are another option to improve glucose tolerance and reduce metabolic damage evoked by hyperglycemia.[46] Moreover, these interventions can simultaneously activate cellular repair processes. Candidate strategies include intermittent fasting and feeding, ketogenic diets, and ketone supplements. Outside the context of critical illness, such interventions have been shown to reduce blood glucose concentrations and/or have an insulin-sparing effect.[46] However, large-scale RCTs studying the efficacy and safety of such interventions in critically ill patients are lacking. RCTs on intermittent versus continuous nutrition have not shown an unequivocal benefit. However, these RCTs were likely too small to detect or exclude a meaningful benefit, and the fasting interval (in general, only 4–6 hours) may have been too short to induce a fasting response and its associated benefits.[73,74] In this regard, pilot RCTs in critically ill adults (N = 70) and children (N = 140) have shown that 12 hours fasting in adults, and 8 to 12 hours in children, only induced a modest metabolic fasting response.[75,76] Although extending the fasting interval may be a theoretic option, this would imply a proportional reduction of the feeding interval, leading to substantial shifts in fluid and glucose administration over a short time period, which is likely poorly tolerated. Ketogenic diets and ketone supplements are alternative strategies. Recently, 2 small pilot RCTs (N = 29 and N = 40) have shown feasibility of a ketogenic diet in critically ill patients, with reduced blood glucose concentrations and insulin need.[77,78] However, whether this translates into a clinical benefit remains to be studied in an adequately powered RCT. Moreover, it remains unclear whether general ICU patients can sufficiently activate ketogenesis, as studies have shown that the inflammatory response to critical illness can result in blunted ketogenesis, and a considerable number of drugs may contain carbohydrates, hampering induction of stable ketosis.[79–81] Regarding ketone administration, animal studies found a protective effect against muscle weakness, which appeared to be explained by signaling effects that involved improved muscle regeneration.[45,82] A small pilot RCT (N = 12) suggested the feasibility of single-dose ketones in patients with cardiogenic shock. Further research is needed to confirm the efficacy and safety of exogenous ketones in patients.[83]

SUMMARY

In conclusion, the ideal blood glucose target in the ICU is likely context-dependent. Severe hyperglycemia and hypoglycemia should be avoided in all critically ill patients. Although tight blood glucose control (80–110 mg/dL [4.4–6.1 mmol/L]) is likely superior from a scientific perspective, safe implementation requires a protocol that avoids hypoglycemia and large blood glucose variability. In the absence of a

validated TGC protocol, it seems advisable to target intermediate blood glucose targets (<150–180 mg/dL [<8.3–10.0 mmol/L]), unless the patient can eat, has no arterial or central venous line, and/or the team is not experienced with such control; in this case, liberal blood glucose control is indicated (<185–215 mg/dL [<10.3–11.9 mmol/L]). Cumulative evidence from glucose control RCTs corroborates the evidence against early parenteral nutrition in ICU patients, and suggests avoiding other iatrogenic causes of hyperglycemia if possible. Future research should study subpopulations of patients who may respond differently to glucose control regimens, and investigate alternative strategies to improve blood glucose control without the need for exogenous insulin.

CLINICS CARE POINTS

- We recommend preventing severe and iatrogenic hyperglycemia (≥185–215 mg/dL [≥10.3–11.9 mmol/L]) in all critically ill patients, as well as severe hypoglycemia (<40 mg/dL [<2.2mmol/L]) and large blood glucose fluctuations.
- We recommend avoiding early full nutrition in all critically ill patients, and initiating parenteral nutrition only after one week in the intensive care unit if the feeding target cannot be reached via the oral or enteral route.
- In patients unable to eat and in need of a central venous and arterial line, we recommend to measure blood glucose (and potassium) at least 1–4 hourly (depending on the clinical evolution and the stability of the measurement) using an accurate blood gas analyzer on arterial blood, and to keep blood glucose at least below 150-180 mg/dL (8.3–10.0 mmol/L) with (if needed) continuous intravenous infusion of short-acting insulin through a central venous catheter; otherwise, we recommend to initiate insulin only when blood glucose exceeds 185–215 mg/dL (10.3–11.9 mmol/L).
- In patients unable to eat and in need of a central venous and arterial line, we recommend to measure blood glucose (and potassium) at least 1–4 hourly (depending on the clinical evolution and the stability of the measurement) using an accurate blood gas analyzer on arterial blood, and to consider tight blood glucose targets (80–110 mg/dL [4.4–6.1 mmol/L]) only if this can be achieved with a validated protocol that does not increase the risk of hypoglycemia.
- In the absence of new evidence, we do not recommend differential blood glucose targets in particular subgroups of patients.

DISCLOSURE

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